Neurobiology of Aging 36 (2015) 1083–1090

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Sleep spindles in Parkinson's disease may predict the development of dementia

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ARTICLE INFO

Article history:
Received 14 April 2014
Received in revised form 6 September 2014
Accepted 10 September 2014
Available online 18 September 2014

Keywords:
Parkinson's disease
Electroencephalography
Non-rapid eye movement sleep
Cognition
Dementia

ABSTRACT

Sleep disturbances and cognitive impairment are common non-motor manifestations of Parkinson's disease (PD). Recent studies suggest that sleep spindles and slow waves play a role in brain plasticity mechanisms and are associated with cognitive performance. However, it remains unknown whether these sleep parameters could serve as markers of cognitive decline in PD. Therefore, we examined whether alterations in sleep spindles and slow waves at baseline visit were associated with increased likelihood of developing dementia at follow-up in PD. Sixty-eight nondemented PD patients (64.9 ± 8.8 years old; 46 men) participated in the study, along with 47 healthy individuals (65.0 ± 10.6 years old; 30 men). All participants underwent baseline polysomnographic recording and a comprehensive neuropsychological assessment. Sleep spindles (12–15 Hz) and slow waves (>75 μV and <4 Hz) were automatically detected on all-night non-rapid eye movement sleep electroencephalography. At follow-up (mean: 4.5 years later), 18 PD patients developed dementia (70.2 ± 7.6 years old; 13 men) and 50 remained dementia-free (63.0 ± 8.5 years old; 33 men). Sleep spindle density and amplitude were lower in PD patients who converted to dementia compared with both patients who remained dementia-free and controls, mostly in posterior cortical regions ($p < 0.05$). Dementia-free PD patients were intermediate between dementia patients and controls, with lower baseline sleep spindle density in all cortical areas compared with controls ($p < 0.01$). In demented PD patients, lower sleep spindle amplitude in parietal and occipital areas was associated with poorer visuospatial abilities. Although slow wave amplitude was lower in PD patients compared with controls ($p < 0.0001$), no difference was observed between those who developed or did not develop dementia. Results demonstrate non-rapid eye movement sleep electroencephalographic abnormalities in PD patients. Sleep spindle activity was particularly impaired in PD patients who developed dementia, with a more posterior topographic pattern. Sleep spindle alterations are associated with later development of dementia in PD, and thus may serve as an additional marker of cognitive decline in these patients.

1. Introduction

Nonmotor symptoms, such as autonomic, neuropsychiatric, sensory, sleep, and cognitive dysfunctions, are now recognized as central features of Parkinson's disease (PD; Chaudhuri et al., 2006, 2011). In cross-sectional studies, approximately one-third of PD patients have dementia (Aarsland and Kurz, 2010). Prospective studies have reported that over 20 years of the disease, up to 75% of PD patients eventually develop dementia (Hely et al., 2008). Certain risk factors (age, depression, apathy, hallucinations, mild cognitive impairment, rapid eye movement sleep behavior disorder [RBD], and akinetic-rigid subtype of PD) and biomarkers (electroencephalography [EEG], magnetic resonance imaging, magnetoencephalography, and genetic anomalies) of dementia have been identified in PD (Aarsland and Kurz, 2010;

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http://dx.doi.org/10.1016/j.neurobiolaging.2014.09.009

Klassen et al., 2011; Olde Dubbelink et al., 2014; Postuma et al., 2012; Svenningsson et al., 2012). However, it remains unknown whether specific EEG sleep characteristics could predict cognitive decline in PD.

There is increasing evidence for a relationship between sleep and cognition in normal and pathologic aging (Fogel et al., 2012). EEG events during non-rapid eye movement (N-REM) sleep, including slow waves (>75 μV and <4 Hz) and sleep spindles (approximately 12–15 Hz), may contribute to brain plasticity (Fogel et al., 2012; Lafortune et al., 2014; Schabus et al., 2006; Steriade, 2006). Recent studies in patients with mild cognitive impairment and Alzheimer's disease found altered N-REM sleep EEG characteristics (Rauchs et al., 2008; Westerberg et al., 2012). To date, few studies have investigated N-REM sleep oscillations in PD, with inconsistent results. Most found lower sleep spindles in PD patients (Christensen et al., 2014; Emser et al., 1988; Puca et al., 1973), except for one (Happe et al., 2004), and none investigated slow waves in this population. Some studies had methodological shortcomings (e.g., no healthy control group, EEG analyses performed only during a portion of the night, use of visual detection only for sleep spindles, PD not diagnosed according to standard clinical criteria and so forth), and none determined whether sleep spindles differed with scalp topography or whether they were related to cognitive status. Because N-REM sleep oscillations are associated with cognitive functioning, their alteration might predict dementia development in PD.

The aim of this study was to examine whether baseline N-REM sleep EEG alterations are associated with increased likelihood of developing dementia on prospective follow-up assessment in PD patients.

2. Methods

2.1. Participants

Patients were recruited from our ongoing longitudinal study on sleep in PD. All patients who underwent a baseline neuropsychological examination and one night of polysomnographic recordings in the sleep laboratory with at least 1 follow-up examination at a minimum of 2 years after the baseline visit were included in the study. Control subjects were recruited by word of mouth and through newspaper advertisements (and were used for baseline comparisons only). The hospital's ethical committee approved the study, and all participants gave their written informed consent before participating.

For inclusion, all patients had to have a clinical diagnosis of PD confirmed by movement disorder specialists according to the criteria of the UK Parkinson's Disease Society Brain Bank, combined with clinical judgment (Hughes et al., 1992). Exclusion criteria were as follows: (1) baseline dementia according to the neuropsychological assessment and the DSM-IV-TR criteria for controls (American Psychiatric Association, 2000), or the recommendations of the Movement Disorder Society Task Force for PD patients (Dubois et al., 2007); (2) major psychiatric disorders according to DSM-IV-TR criteria (American Psychiatric Association, 2000); (3) history of head injury, stroke, or cerebrovascular disease; and (4) abnormal EEG features suggesting epilepsy. Patients were taking their usual medication during the study (see Table 1 for data on dopaminergic drugs). Some patients were also taking other anti-parkinsonian medication (i.e., amantadine, selegiline; PD-dementia, n = 3; PD-no dementia, n = 25), acetylcholinesterase

Table 1
Baseline demographic, clinical, and polysomnographic characteristics

Characteristics	PD-dementia n = 18	PD-no dementia n = 50	Controls n = 47	*p*
	A	B	C	
Sex, % men	72	66	64	0.82
Age, y	70.2 ± 7.6	63.0 ± 8.5	65.0 ± 10.6	0.02; A > B
Education, y	14.4 ± 3.8	14.3 ± 4.1	14.1 ± 3.8	0.94
Follow-up duration, y	4.6 ± 1.5	3.9 ± 1.8	—	0.15
Disease duration, y[a]	5.7 ± 4.5	4.1 ± 3.1	—	0.26
Hoehn & Yahr stage	2.8 ± 0.9	2.1 ± 0.8	—	0.007
UPDRS part III "on"	21.5 ± 12.5	22.8 ± 10.1	—	0.67
Levodopa equivalent dosage, mg	645.6 ± 335.3	416.2 ± 319.2	—	0.01
Levodopa use, n (%)	15 (83)	41 (82)	—	0.90
Dopamine agonist use, n (%)	5 (28)	17 (34)	—	0.63
Medication other than dopaminergic, %[b]	42	50	—	0.56
REM sleep behavior disorder, n (%)	16 (89)	20 (40)	—	0.0001
Mild cognitive impairment, n (%)	16 (89)	21 (42)	—	0.001
Beck Depression Inventory[c]	12.7 ± 9.4 n = 18	9.6 ± 5.8 n = 45	5.8 ± 5.8 n = 44	0.0002; A > C, B > C
Beck Anxiety Inventory[c]	13.9 ± 11.2 n = 17	9.5 ± 6.1 n = 46	5.3 ± 6.0 n = 32	0.0005; A > C, B > C
Polysomnographic				
Latency to persistent sleep, min[c]	42.9 ± 14.0	27.5 ± 3.6	37.0 ± 6.6	0.57
Total sleep time, min	338.3 ± 134.2	357.1 ± 80.9	380.3 ± 63.7	0.16
Total apnea-hypopnea index[c]	2.7 ± 3.8	7.5 ± 9.2	3.2 ± 3.8	0.07
Sleep efficiency, %[c]	72.6 ± 20.7	77.3 ± 15.5	83.4 ± 10.0	0.08
Stage 1, %[c]	13.0 ± 9.8	13.3 ± 8.5	10.0 ± 5.4	0.12
Stage 2, %	58.3 ± 7.2	63.8 ± 11.3	64.4 ± 7.0	0.05; A < C
Slow wave sleep, %	10.5 ± 8.3	7.0 ± 8.7	7.5 ± 7.3	0.28
REM sleep, %[c]	18.2 ± 12.8	16.0 ± 7.2	18.0 ± 4.6	0.25

Results are expressed as mean ± standard deviation.
Key: ANOVA, analysis of variance; PD-dementia, Parkinson's disease patients who developed dementia; PD-no dementia, Parkinson's disease patients who remained dementia-free; REM, rapid eye movement; UPDRS, Unified Parkinson's Disease Rating Scale.
[a] U Mann-Whitney test.
[b] See text for details on nondopaminergic PD medication.
[c] Kruskal-Wallis ANOVA.

inhibitors (PD-dementia, n = 3; PD-no dementia, n = 0), antidepressants (PD-dementia, n = 3; PD-no dementia, n = 9), or benzodiazepines (PD-dementia, n = 2; PD-no dementia, n = 10). Control subjects were not taking any medication known to influence sleep during the study. The Hoehn and Yahr scale and part III of the Unified Parkinson's Disease Rating Scale were used to assess disease and motor severity in patients (Fahn and Elton, 1987; Hoehn and Yahr, 1967). Most participants (see Table 1 for numbers in each group) also completed the Beck Depression Inventory, Second Edition (BDI-II) and the Beck Anxiety Inventory (BAI) to assess depression and anxiety symptoms (Beck et al., 1961, 1988).

2.2. Procedures

2.2.1. Cognitive assessment

All subjects underwent a comprehensive neuropsychological assessment at baseline visit. Five cognitive domains were assessed: attention, executive functions, episodic memory, visuospatial abilities, and language (neuropsychological tests, variables, and normative data are presented in Supplementary Table A1). At follow-up, all patients were offered a comprehensive neuropsychological assessment. Cognitive and/or dementia status was determined by consensus between the neuropsychologist (Jean-François Gagnon) and neurologist (Ronald B. Postuma), and dementia diagnosis was established according to Movement Disorder Society Task Force criteria, defined as impairment on at least 2 cognitive domains on neuropsychological testing, with evidence of significant functional impact on daily living activities (Dubois et al., 2007; see footnote to Supplementary Table A1; underlined tests were included in the follow-up examination battery). Mild cognitive impairment status at baseline was determined by consensus between the neuropsychologist and neurologist according to published criteria (Gagnon et al., 2009; Litvan et al., 2012). Impairment in daily functioning was determined during the interview with participants and their relatives when available by significant alterations (i.e., patient can no longer execute the task or else needs help by others) in several activities such as the ability to manage finances, perform chores, clean the house, prepare meals, do the shopping, drive the car, or use public transportation. Patients were also questioned about their use of medications to assess daily living functioning and mental organization, including the ability to clearly describe their medication (i.e., drug, dose, and timing) and whether they can organize and take it independently (questions were derived from the Pill Questionnaire appended to Dubois et al., 2007). If patients refused or were unable to come for the neuropsychological follow-up assessment, bedside clinical tests such as the Mini-Mental State Examination or the Montreal Cognitive Assessment were performed (Folstein et al., 1975; Nasreddine et al., 2005). Patients unable to be assessed in-person (e.g., severe disability and/or dementia) were followed up by telephone, with the patient and/or spouse, or cases were reviewed with the treating physician.

2.3. Polysomnographic recording

The polysomnographic montage included frontal (F3, F4), central (C3, C4), parietal (P3, P4), and occipital (O1, O2) EEG leads with linked ears reference at 10 kΩ resistance, a bilateral electrooculogram, and chin electromyographic recordings. Respiration was monitored using a nasal canula or a nasal and/or oral thermistor with thoracic and abdominal strain gauges. Polysomnography was recorded with a Grass polygraph (amplifier gain 10,000; bandpass 0.3–100 Hz), and signals were digitized at a sampling rate of 256 Hz using Harmonie software version 6.2b (Stellate Systems, Montreal, Quebec, Canada). N-REM sleep stages were visually scored on 20-second epochs according to a modified version of the Rechtschaffen and Kales method (Rechtschaffen and Kales, 1968). REM sleep of PD patients and controls was scored according to a method developed in our laboratory (Lapierre and Montplaisir, 1992; Montplaisir et al., 2010). RBD in PD patients was diagnosed according to standard clinical and polysomnographic criteria (American Academy of Sleep Medicine, 2005; Montplaisir et al., 2010). Polysomnographic variables included latency to persistent sleep, total sleep time, total apnea-hypopnea index (number per hour), sleep efficiency, and sleep stage percentages.

2.4. N-REM sleep oscillations

All EEG analyses were performed on left and right parasagittal derivations (F3, F4, C3, C4, P3, P4, O1, and O2). Electromyographic artifacts were automatically and visually detected and then rejected before analysis (Brunner et al., 1996). Sleep spindles were detected in artifact-free epochs using previously published criteria (Lafortune et al., 2014; Martin et al., 2013). EEG data were bandpass filtered between 11.1 and 14.9 Hz using a linear phase finite impulse response filter (−3 dB at 11.1 and 14.9 Hz). Data were forward and reverse filtered to obtain zero-phase distortion and to double the filter order. The root mean square of the filtered signal was then calculated with a 0.25-second time window and thresholded at the 95th percentile. A sleep spindle was detected when at least 2 consecutive root mean square time points exceeded the threshold duration criterion (0.5 seconds). The mean duration of all-night sleep spindles was 0.63 ± 0.04 seconds. Individual sleep spindle characteristics were derived and averaged over all-night N-REM sleep: density (number/minute), amplitude (expressed in μV), and frequency (number of cycles/second, expressed in Hz). Supplementary analyses were performed on previously detected sleep spindles to identify slow (11.99–12.99 Hz) and fast (13.00–14.99 Hz) spindles (see Supplementary Methods).

Slow waves were automatically detected in artifact-free epochs using criteria described elsewhere (Carrier et al., 2011; Latreille et al., 2011). EEG data were bandpass filtered between 0.1 and 4.0 Hz using a linear phase finite impulse response filter (−3 dB at 0.1 and 3.99 Hz). Individual slow wave characteristics were derived and averaged over all-night N-REM sleep: density (number/minute), amplitude (peak-to-peak, expressed in μV), and slope (expressed in μV/millisecond).

2.5. Statistical analyses

One-way analyses of variance, independent sample *t* tests, and Pearson χ^2 tests were performed to assess differences between PD patients with dementia, PD patients without dementia, and controls on demographic, clinical, polysomnographic, and cognitive data. Nonparametric equivalent tests or logarithmic transformations were used for abnormally distributed variables. Preliminary analyses of variance with 3 groups and 1 repeated measure (2 hemispheres: left and right) were first computed on each derivation (F3, F4, C3, C4, P3, P4, O1, and O2) to identify significant group-hemisphere interactions for sleep spindle and slow wave characteristics. Because no significant group-hemisphere interaction was found, results for each hemisphere were averaged. One-way analysis of covariance (ANCOVAs), with group as a factor (3 groups: PD with dementia, PD without dementia, and controls) and one repeated measure (4 derivations: frontal, central, parietal, and occipital) were then performed to compare sleep spindle and slow wave characteristics. Age was used as a covariant in the analyses, given that N-REM sleep oscillations are influenced by age (Carrier et al., 2011). *p*-values were adjusted for sphericity with the Huynh-Feldt correction for repeated measures with more than 2

levels, but original degrees of freedom are reported. Mean comparison analyses were performed with Tukey post hoc test for significant main effects, and simple effect analyses were used to interpret significant interactions. We performed receiver operator characteristic (ROC) curves to assess the sensitivity and specificity of sleep spindle density and amplitude to predict dementia development in PD patients. The optimal cutoff value was defined as the highest combined sensitivity and specificity score. Pearson correlations or nonparametric Spearman rank correlations for variables not normally distributed were also performed to examine relationships between sleep spindle characteristics and clinical variables and between sleep spindle characteristics and cognitive measures in PD patients. Correlations between sleep spindles and neuropsychological tests were performed in the 2 PD groups separately to determine which cognitive measure is precisely associated with sleep spindle anomalies in patients at risk of developing dementia (we also performed correlations between these variables in all PD patients, and results are presented in Supplementary Results). To reduce the number of correlations in the neuropsychological data, we computed composite scores for each cognitive domain using averaged z scores (see Supplementary Methods for details on cognitive composite scores). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic, clinical, and polysomnographic characteristics

Initially, 82 patients were enrolled in the baseline cohort. Fourteen patients (17%) could not be assessed at follow-up: 8 had died, 2 refused the reassessment, and 1 was unreachable. Moreover, baseline EEG recordings for 3 patients were unusable for analysis because of significant artifacts. Consequently, 68 PD patients (83%) met inclusion criteria and were prospectively followed; 41 patients (60%; 17% developed dementia and 83% remained dementia-free) underwent a comprehensive neuropsychological assessment at follow-up, 18 patients (26%; 50% developed dementia and 50% remained dementia-free) had office-based cognitive testing by an expert neurologist, and 9 patients (13%; 22% developed dementia and 78% remained dementia-free) were followed up by telephone. At follow-up, 18 patients (26%) developed dementia (Table 1). PD patients who converted to dementia were older than patients who remained dementia-free at baseline visit. Compared with PD patients without dementia, PD patients who developed dementia had a higher Hoehn and Yahr stage, took higher levodopa doses, and were more likely to have mild cognitive impairment and RBD at baseline. Sex, education, follow-up duration, disease duration, part III of the Unified Parkinson's Disease Rating Scale, and the proportion of patients taking levodopa, dopamine agonist, or nondopaminergic medication at baseline did not differ between PD with and without dementia at follow-up. BDI and BAI scores were higher in both patient groups compared with controls. On the polysomnographic variables, PD patients who developed dementia had lower percentage of stage 2 sleep at baseline than controls.

3.2. Sleep spindle characteristics

As shown in Fig. 1, significant interactions were found between groups and derivations for sleep spindle density ($F[6,333] = 3.2$; $p < 0.01$), and amplitude ($F[6,333] = 3.9$; $p < 0.004$). PD patients who developed dementia had lower sleep spindle density in all cortical

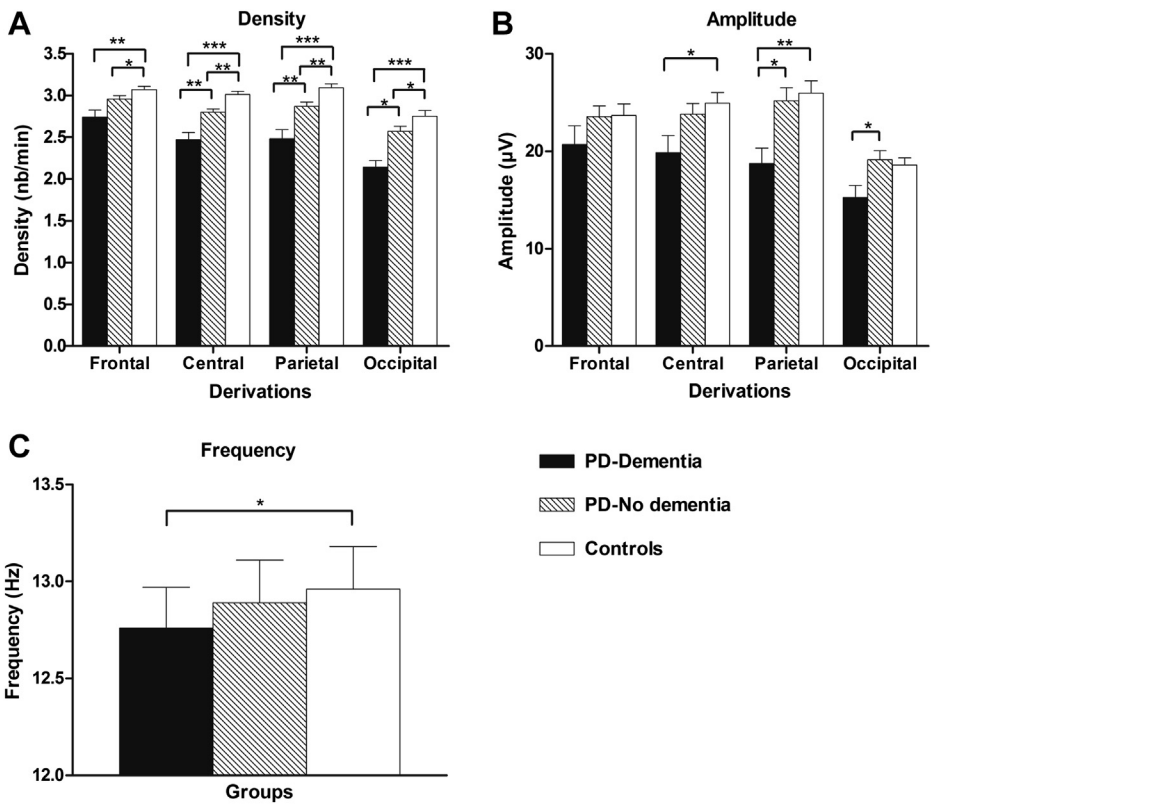

Fig. 1. Sleep spindle characteristics in PD patients who developed dementia, PD patients who remained dementia-free, and controls; Sleep spindle density (A), amplitude (B), and frequency (C). Contrast analyses: $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.0001$. Results are log transformed and expressed as mean (±SEM). Abbreviations: PD, Parkinson's disease; SEM, standard error of the mean.

areas than controls at baseline. Furthermore, compared with PD patients who remained dementia-free, patients who converted to dementia had lower sleep spindle density at baseline in the central, parietal, and occipital regions. Compared with controls, PD patients who remained dementia-free had lower sleep spindle density at baseline in all cortical areas. PD patients who developed dementia also had lower sleep spindle amplitude at baseline compared with controls in the central and parietal areas. Comparing the 2 PD groups, patients who developed dementia showed lower sleep spindle amplitude in parietal and occipital areas. Sleep spindle amplitude did not differ between non-converted PD patients and controls. A significant group effect was found for sleep spindle frequency (F[2,111] = 3.7; $p < 0.03$), with post hoc comparisons showing significantly lower sleep spindle frequency in PD patients who developed dementia compared with controls.

Because PD patients who developed dementia had slightly lower sleep stage 2 percentage ($p = 0.05$) compared with controls, we performed supplementary correlations between sleep spindle characteristics and sleep stage 2 percentage in all participants. We found no significant correlation with sleep spindle amplitude or frequency, but a weak correlation was found with sleep spindle density in occipital regions only ($r = 0.19$, $p = 0.04$). However, the same results as reported previously were found for sleep spindle density when sleep stage 2 percentage was used as a covariant (with age) in the ANCOVA. ANCOVAs controlling for Hoehn and Yahr, levodopa dosage, or the use of acelylcholinesterase inhibitors did not significantly change the results (see Supplementary Methods). Results for slow and fast sleep spindle density are presented in Supplementary Results.

3.2.1. Sleep spindle characteristics and cognitive measures

At baseline, PD patients who developed dementia scored significantly lower on measures of attention, executive functions, episodic memory, and visuospatial abilities compared with both PD patients who remained dementia-free and controls (Table 2). PD patients who remained dementia-free also scored lower on measures of attention and executive functions compared with controls. In the PD-dementia group, higher visuospatial scores were associated with higher sleep spindle amplitude in parietal and occipital areas ($r = 0.49$, $p = 0.04$ and $r = 0.51$, $p = 0.03$, respectively). No other significant correlations were found between composite scores and sleep spindles in each PD group.

3.2.2. Sensitivity and specificity analyses

Using the ROC curve analysis, the optimal cutoff value for sleep spindle density in occipital regions was 2.3, with 78% sensitivity and 64% specificity (area under the curve = 0.79 [95% CI: 0.67–0.91], $p = 0.0001$). For sleep spindle amplitude in parietal regions, a 22.6 cutoff showed 83% sensitivity and 60% specificity (area under the curve = 0.73 [95% CI: 0.60–0.86], $p = 0.004$).

3.3. Slow wave characteristics

Significant group effects were found for slow wave amplitude (F[2,110] = 113.0; $p < 0.0001$), with post hoc comparisons showing lower amplitude in both PD groups compared with controls (Fig. 2). Slow wave amplitude did not differ between PD groups. A significant group-derivation interaction was found for slow wave slope (F[6,330] = 3.7; $p < 0.01$) but contrast analyses failed to reach significance. No significant group effects or group-derivation interactions were found for slow wave density.

4. Discussion

Compared with both healthy controls and patients who remained dementia free, PD patients who later developed dementia showed marked sleep spindle alterations at baseline, including lower sleep spindle density and amplitude, mainly in posterior cortical regions. Sleep spindle frequency was also lower in PD patients who developed dementia compared with controls, and supplementary analyses showed that fast sleep spindles were altered in PD patients with dementia, with a global effect across all cortical derivations. Moreover, lower sleep spindle amplitude in posterior areas was associated with poorer visuospatial abilities only in PD patients who developed dementia. Slow wave amplitude was also altered in PD patients but did not differ between patients according to their cognitive status at follow-up. These results suggest that impaired sleep spindle activity is associated with dementia development in PD.

Only a few studies have investigated sleep spindles in PD, with inconsistent results (Christensen et al., 2014; Emser et al., 1988; Happe et al., 2004; Puca et al., 1973). Some of these studies also had methodological shortcomings, as they did not include a healthy control group for comparison (Puca et al., 1973), EEG analyses were performed on only a portion of the night (Happe et al., 2004), or sleep spindles were detected visually (Emser et al., 1988; Happe et al., 2004; Puca et al., 1973). A recent study by Christensen et al. (2014) found lower sleep spindle density in PD patients compared with age-matched controls, but no difference between patients according to the presence of RBD. For comparison purposes, we performed supplementary analyses to examine baseline sleep spindle density in PD patients with or without RBD and controls, regardless of dementia status. Similar to the findings of Christensen et al. (2014), patients with PD had lower sleep spindle density but sleep spindles did not significantly differ according to RBD status. None of these studies considered patients' cognitive status. Our results show that sleep spindle anomalies in PD are related mainly to cognitive decline.

Our results support a growing body of evidence linking sleep spindles to cognition in adults and healthy elders (Fogel et al., 2012; Lafortune et al., 2014; Schabus et al., 2006). Recent studies in

Table 2
Cognitive performances on neuropsychological tests at baseline

Composite scores	PD-dementia	PD-no dementia	Controls	p
	A	B	C	
Attentional	−1.27 ± 0.87	−0.35 ± 0.78	0.17 ± 0.58	0.00001; A < B; B < C; A < C
Executive functions[a]	−2.13 ± 1.92	−0.58 ± 0.90	0.00 ± 0.64	0.00001; A < B; B < C; A < C
Episodic memory	−0.99 ± 0.67	0.13 ± 1.22	0.43 ± 0.88	0.00001; A < B; A < C
Visuospatial	−1.06 ± 0.70	0.05 ± 0.88	0.35 ± 0.92	0.00001; A < B; A < C
Language[a]	−0.07 ± 0.59	0.06 ± 1.35	−0.63 ± 0.53	0.09

Results are presented as mean z score ± standard deviation.
Key: ANOVA, analysis of variance; PD-dementia, Parkinson's disease patients who developed dementia; PD-no dementia, Parkinson's disease patients who remained dementia-free.
[a] Kruskal-Wallis ANOVA.

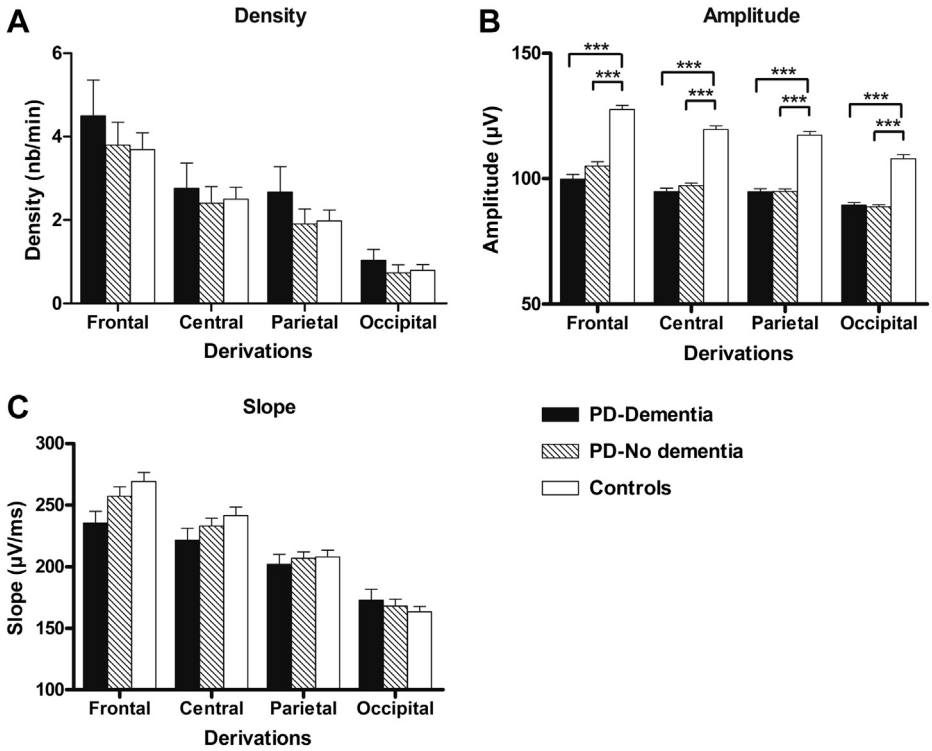

Fig. 2. Slow wave characteristics in PD patients who developed dementia, PD patients who remained dementia-free, and controls; Slow wave density (A), amplitude (B), and slope (C). Contrast analyses: $^{***}p < 0.0001$. Results are log transformed and expressed as mean (±SEM). Abbreviations: PD, Parkinson's disease; SEM, standard error of the mean.

patients with mild cognitive impairment and Alzheimer's disease have associated cognitive decline with altered sleep spindle activity (Rauchs et al., 2008; Westerberg et al., 2012). Amnestic mild cognitive impairment patients showed lower sleep spindles in frontal cortical areas and lower sigma-frequency spectral power (12.5–15.5 Hz) in parietal areas (Westerberg et al., 2012). Alzheimer's disease patients also showed lower fast spindles (13–15 Hz) but in central regions only (Rauchs et al., 2008). In line with these findings, we also found lower fast sleep spindles (13–15 Hz) in PD patients who developed dementia compared with those who remained dementia-free and controls (see Supplementary Results), but this effect did not differ across cortical derivations. Thus, reduced fast sleep spindles may serve as an additional sign of cognitive decline in PD.

Considering the whole frequency range of sleep spindles (12–15 Hz), our results show a more extensive posterior (vs. anterior) topographic pattern of sleep spindle anomalies in PD patients who develop dementia. ROC curve analysis was computed to assess the sensitivity and specificity of sleep spindle density and amplitude to predict dementia development in PD patients. Results showed that sleep spindle density in occipital regions and sleep spindle amplitude in parietal regions had the highest predictive sensitivity (0.78 and 0.83, respectively) and specificity (0.64 and 0.60, respectively) for dementia development in PD patients. Areas under the curves showed that optimal cutoff values for sleep spindle density and amplitude could be qualified as "fairly good." However, these results lacked statistical power, given the small number of patients in the dementia group, and further analyses in a much larger sample of patients are needed.

Moreover, we found that lower sleep spindle amplitude in posterior regions was associated with poorer visuospatial abilities in patients who developed dementia at follow-up. In all PD patients together (see Supplementary Results), sleep spindle density and amplitude in frontal, central, and posterior regions were positively associated with performances on measures of executive functions. Visuospatial measures were also positively associated with sleep spindle amplitude in occipital regions, and finally, attentional measures correlated with sleep spindle frequency in frontal regions. Obviously, in regards to the current literature, one would have expected to find an association between sleep spindles and declarative memory (Fogel et al., 2012; Schabus et al., 2006). However, this was not the case in our PD cohort. Nevertheless, our results are in line with studies suggesting that visuospatial deficits related to posterior cerebral regions are associated with earlier cognitive decline and dementia onset in PD patients (Kehagia et al., 2010; Litvan et al., 2012; Williams-Gray et al., 2009). Our findings are also in agreement with several studies investigating potential markers of cognitive impairment (EEG, magnetoencephalography, magnetic resonance imaging, and fMRI) in PD that found a prominent posterior pattern of dysfunction (Eidelberg, 2009; Klassen et al., 2011; Olde Dubbelink et al., 2014; Svenningsson et al., 2012).

In our study, although PD patients who remained dementia-free at follow-up did not differ from controls on several N-REM sleep variables, they had intermediate values between patients who developed dementia and controls for sleep spindle density in posterior cortical regions. Because a large proportion of PD patients will develop dementia over time (Hely et al., 2008), patients with lower sleep spindle activity might still be at risk for ultimately developing dementia.

At the cellular level, sleep spindles originate from the oscillatory activity of the thalamo-cortical loop (Steriade, 2006). They are generated by the rhythmic activity of inhibitory postsynaptic potentials fired by reticular thalamic neurons toward thalamo-cortical cells. Through this periodic and recurrent activity, sleep spindles appear to support brain plastic changes underlying learning and memory consolidation, notably via mechanisms such as long-term potentiation (Fogel et al., 2012). Because sleep spindle activity is prominently impaired in PD, the mechanisms underlying brain

plasticity could be greatly altered and may trigger some of the cognitive impairment in these patients.

In PD, structural and functional alterations in the thalamus, brainstem structures, and posterior brain regions have been identified in neuroimaging and neuropathologic studies (Halliday et al., 2011; Jellinger, 2012; Menke et al., 2014; Svenningsson et al., 2012). In vivo neuroimaging studies found early reductions in cholinergic neurotransmission in PD (Bohnen and Albin, 2011; Kotagal et al., 2012; Shimada et al., 2009; Ziabreva et al., 2006) and widespread reductions in acetylcholinesterase activity occur even in early PD, particularly in the parietal and occipital cortical regions (Bohnen and Albin, 2011; Shimada et al., 2009). These cholinergic deficits worsen with the appearance of dementia (Bohnen and Albin, 2011; Shimada et al., 2009). In PD-dementia, additional reductions in choline acetyltransferase activity occur in the reticular thalamic nuclei (Ziabreva et al., 2006). Of interest, administration of donepezil, an acetylcholinesterase inhibitor, restored previously absent sleep spindle activity during N-REM sleep in a patient with dementia with Lewy bodies (Ozaki et al., 2012). Similarly, in a study of 42 healthy elderly subjects, donepezil intake increased sigma activity during N-REM sleep stage 2 (Hornung et al., 2009). Therefore, in PD and especially in association with cognitive impairment, the prominent cholinergic depletion observed as well as the presence of structural and functional cortical alterations (mainly in posterior areas) might significantly disturb the cortico-thalamic feedback loop and therefore alter sleep spindle generation mechanisms.

Slow wave amplitude was altered at baseline in PD patients, regardless of dementia status at follow-up. This suggests that slow waves are less predictive than sleep spindles for cognitive performance (Lafortune et al., 2014). Slow wave amplitude could potentially be greatly affected by the large-scale neural loss associated with the disease. This should be explored in future neuroimaging studies using measures such as cortical thickness in PD. Recent polysomnographic studies in early PD patients show no major sleep macrostructural alterations compared with aged controls (Diederich et al., 2013; Peeraully et al., 2012). We found similar results, except for sleep stage 2 percentage, which was slightly lower in PD patients who developed dementia compared with controls (without differences among PD patients who did or did not develop dementia). Group differences in stage 2 sleep percentage, disease progression, levodopa dose, use of anticholinesterase drugs, and BDI and BAI scores do not appear to explain our main results.

Limitations of this study should be noted. First, cognitive and/or dementia status at follow-up was determined in 27 PD patients (40%) by either brief clinical tests, case reviews with the treating physician, or telephone follow-up with patients and/or spouses. Consequently, not all patients underwent comprehensive neuropsychological follow-up assessment. However, for those patients who were unable to participate in an in-person evaluation, many had severe disability and some were institutionalized. Cognitive and/or dementia status was determined by consensus between the neurologist, neuropsychologist, and treating physician when necessary. We performed supplementary analyses in the subgroup of patients who underwent a complete neuropsychological evaluation at follow-up (PD-dementia, $n = 7$, and PD-no dementia, $n = 34$; see Supplementary Methods). Although the PD-dementia group was small, we still observed significant effects on sleep spindle density, with dementia patients showing lower sleep spindle density compared with those who remained dementia-free. Therefore, evaluation type at follow-up does not appear to influence our main results, and we remain relatively confident in our conclusions regarding dementia diagnosis in our cohort of PD patients. Finally, PD patients were taking their usual medication during the study. It remains unclear whether dopaminergic or nondopaminergic PD medication may influence N-REM sleep mechanisms. Some studies have investigated the impact of dopaminergic medication (levodopa and/or dopamine agonists) on nocturnal sleep and EEG in PD, with inconsistent results, probably because of methodological differences. A few studies reported beneficial (Balaid et al., 2014) or no significant influence of dopaminergic medication on sleep macrostructure (Diederich et al., 2009; Garcia-Borreguero et al., 2002; Wailke et al., 2011), whereas others have shown that dopaminergic medication intake before sleep increases sleep stage 1 and 2 percentage, number of awakenings, and wake time after sleep onset, although it decreases slow wave and REM sleep percentage (Brunner et al., 2002; Chahine et al., 2013; Feld et al., 2014; Kaynak et al., 2005; Sixel-Döring et al., 2012). Further, randomized-controlled trials in large cohorts of PD patients are needed to clarify this important issue.

5. Conclusions

Our results suggest that sleep spindles are considerably impaired in PD, according to a more posterior topographic pattern. Alterations in sleep spindle activity are related to dementia development in PD and are therefore a potential marker of cognitive decline in this population. Future neuroimaging studies should explore the relationships between N-REM sleep oscillations and structural and functional alterations in PD.

Disclosure statement

The authors have no actual or potential conflicts of interest.

Acknowledgements

This study was supported by grants from the Canadian Institutes of Health Research, Canada (MOP-84482; Jean-François Gagnon, Ronald B. Postuma, and Julie Carrier) and the Fonds de Recherche du Québec - Santé, Canada (Jean-François Gagnon, Ronald B. Postuma, and Julie Carrier). Véronique Latreille and Josie-Anne Bertrand were supported by a scholarship from the Canadian Institutes of Health Research, Canada, and Marjolaine Lafortune was supported by a scholarship from the Fonds de Recherche du Québec - Santé, Canada.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2014.09.009.

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